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Received: 23 March 2020 | Revised: 22 September 2020 | Accepted: 18 October 2020

DOI: 10.1111/tbed.13889

ORIGINAL ARTICLE

Transboundary and Emerging Diseases WILEY

Feline tuberculosis caused by *Mycobacterium bovis* infection of domestic UK cats associated with feeding a commercial raw food diet

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Funding information
Biotechnology and Biological Sciences Research Council, Grant/Award Number: BB/M014894/1; Biotechnology and Biological Sciences Research Council, Grant/Award Number: M014894, 1, M010996, 1, P013740, 1 and 20002174

Abstract

Mycobacterium (M.) bovis can infect cats and is a demonstrated zoonosis. We describe an outbreak of *M. bovis* in pet cats across England and Scotland associated with feeding a commercial raw food diet. Forty-seven cats presented with (pyo)granulomatous lesions, lymphadenopathy, pulmonary and/or alimentary disease over a one-year period where *M. bovis* infection was suspected or definitively diagnosed, and the cats all consumed the same specific brand of commercial raw venison pet food. Infection with *M. bovis* genotype 10:a was confirmed by culture and DNA typing of isolates in a small number of cases ($n = 5$); PCR was used in combination with or as an alternative to culture ($n = 12$) and/or infection with a *Mycobacterium tuberculosis* complex group organism was strongly suggested by positive responses to an interferon-gamma release assay (IGRA; $n = 34$). Asymptomatic at-risk cats were screened by IGRA, identifying a further 83 infected cats. The five culture-positive cases were distributed across areas of England and Scotland at low risk of endemic bovine tuberculosis. Investigations revealed affected cats were mainly indoor-only, and had been fed the same commercial raw food as at least part of their diet. This diet was recalled by the manufacturer due to failure of statutory meat inspection of the component venison. As far as possible, other sources of infection were explored and excluded, including wildlife contact, access to raw milk and living with people with active *M. bovis* infection. Four owners and one veterinary surgeon were found to have high likelihood of latent tuberculosis infection. One owner required treatment. Although it was not possible to conclusively demonstrate a zoonotic origin for these infections, neither was it possible to eliminate the possibility. Our results provide compelling evidence that the commercial raw diet of these cats was the likely route of *M. bovis* infection in this outbreak of cases.

Jayne Hope and Danièlle Gunn-Moore are joint last authors.

KEYWORDS
companion animals, mycobacterium bovis, raw food diet, tuberculosis

1 | INTRODUCTION

Mycobacterium (M.) bovis is one of the member species of the *Mycobacterium tuberculosis* complex (MTBC) which are capable of causing tuberculosis across a broad taxonomy of species including but not limited to humans, cattle, deer, dogs and cats (Allen, 2017; Phillips et al., 2003; Sales et al., 2001).

Feline infections with *M. bovis* are strongly co-localized to areas of the UK with a high prevalence of infections in cattle (Gunn-Moore et al., 2011b, 2017), termed the high-risk area (HRA) of England by the Department for Environment, Food and Rural Affairs (Defra) and "high TB areas of Wales" by the Welsh Government, 2014. Conversely, feline *M. bovis* infections are very rare in Scotland and the low-risk area (LRA) of England, and have somewhat higher incidence in the edge area located between the LRA and HRA of England as evidenced by a *M. bovis* cluster in cats in Berkshire in 2013 (Roberts et al., 2014).

Within the MTBC group of pathogens, *M. bovis* has the broadest host range and poses a substantial zoonotic risk (Biet et al., 2005; Sales et al., 2001; Suzuki et al., 2010). Disease in humans due to infection with *M. bovis*, termed "zoonotic tuberculosis" by the World Health Organisation (WHO), is a major global public health priority in developing countries which resulted in nearly 150,000 cases and at least 12,500 deaths worldwide in 2010 (World Health Organisation, 2017). Approximately a third of feline mycobacteriosis cases in the UK are caused by MTBC pathogens; in the only published study, *M. microti* was cultured from 19% of all submitted cases of feline mycobacteriosis, and 15% were caused by *M. bovis* (Gunn-Moore et al., 2011a).

Characterisation of the typical clinical manifestations of feline mycobacterial diseases in the UK has shown that 74% of cases present with single or multiple cutaneous lesions, 47% with lymphadenopathy (typically submandibular or popliteal) and 10%–16% with pulmonary or systemic signs (Gunn-Moore et al., 2011a). The remainder of cases are small numbers of relatively rare presentations such as alimentary, joint or ocular mycobacteriosis (Gunn-Moore, 2014; Clarke et al., 2017; Stavinohova, et al., 2019).

We have previously reported on a highly unusual group of 13 confirmed or highly likely *M. bovis* tuberculosis cases in pet cats (O'Halloran, Gunn-Moore, et al., 2018; O'Halloran et al., 2019). Initially, a striking feature was that several of these cases presented with one of the rarest manifestations of disease, alimentary tuberculosis. The investigation became more complex when diagnostic tests indicated *M. bovis* infections, as nearly all of these cats were living in areas of the UK which have either a very low prevalence of *M. bovis* in cattle and badger (such as the North East of England), or Scotland, which holds officially *M. bovis* free status (for cattle) (APHA, 2017; O'Halloran et al., 2019). Suspicions were raised with regard to a possible link to diet as all cats were indoor-only, had no access to alternative sources of infection as far as we could determine, and they were all fed the same commercial raw food product, as either all or part of their diet (Food Standards Agency, 2018; O'Halloran et al., 2019).

We concluded that these initial findings provided circumstantial evidence of an association between the commercial raw diet of these cats and their *M. bovis* infections. Since then, further cases have been diagnosed and an epidemiological investigation undertaken; the purpose of this publication is to outline in full our findings, and conclusions from both the clinical and epidemiological investigations.

2 | CLINICAL INVESTIGATIONS

2.1 | Case definition

For cases to be included in this study, feline *M. bovis* infection was either strongly suspected based on clinical presentation and owner-reported history, combined with a positive interferon-gamma release assay or definitively diagnosed by tissue culture or PCR, and the cat(s) had to have consumed the same raw commercial pet food as part or all of their diet.

2.2 | Clinical presentation of cases

Forty-seven cats from 43 households (Table 1) have been diagnosed with active tuberculous disease linked to this outbreak at the time of writing. All 47 cases were presented to their general practice veterinary surgeons over the course of one year (July 2018 to July 2019). The majority of affected cats (36/47, 76.6%) were pedigree breeds including ten Persians, eight Bengals, five Maine Coons, four British Shorthairs, two Ragdolls and one each of Siamese, Oriental, Abyssinian, Burmese, Toyger, British Blue and one Bengal cross cat. The remaining nine cats were non-pedigrees: eight domestic shorthairs and one domestic longhair. Cases were distributed across England and mainland Scotland (Figure 1).

The age at presentation ranged from three-month-old kittens to 13-year-old adults, with a median age of two years. There was no statistical difference between the number of male or female cats presenting with disease ($X_1^2 = 1.48$, $p > .05$); approximately half of the cats (24/47, 51.0%) were neutered males and ten cats were neutered females (21.3%), whilst nine were entire females (19.1%) and four (8.5%) were entire males.

The clinical signs noted were most frequently non-specific signs of ill health, including combinations of lethargy (18/47 cats, 38.3%), hyporexia and poor or declining body weight/condition (15/47 cats, 31.9%).

TABLE 1 Details of the active cases of tuberculosis in the cats affected in this outbreak

Case No.	Location (county)	Date[a]	Breed	Age	Sex	Positive mycobacterial tests	Clinical sign(s) noted by the owner(s)
1	Durham	July 2018	Siamese	2 years	MN	IGRA	Lethargy, hyporexia and pyrexia
2	Durham	Aug 2018	Oriental	2 years	FN	IGRA	Chronic cough
3	Brighton	Aug 2018	DSH	1 year	FN	PCR and IGRA	Lethargy, hyporexia and weight loss
4	Norfolk	Sept 2018	DLH	1.5 years	MN	PCR and IGRA	Diarrhoea
5	Devon	Oct 2018	Bengal cross	6 years	FN	Culture and PCR	Lethargy and hyporexia
6	Devon	Oct 2018	Abyssinian	4 years	MN	IGRA	Lethargy and hyporexia
7	Essex	Oct 2018	Maine Coon	1.5 years	MN	IGRA	Pyrexia and lymphadenomegaly
8	Norfolk	Nov 2018	Burmese	1.5 years	MN	PCR	Hyporexia and pyrexia
9	Surrey	Nov 2018	British Shorthair	4 months	FE	IGRA	Respiratory distress
10	Dumfries	Dec 2018	Bengal	5 years	FN	Culture and IGRA	Respiratory distress
11	Dumfries	Dec 2018	Bengal	5 years	FN	IGRA	Weight loss
12	Durham	Jan 2019	Toyger	2 years	MN	IGRA	Blindness
13	Aberdeenshire	Feb 2019	Ragdoll	10 months	MN	Culture and IGRA	Respiratory distress
14	Hertfordshire	Feb 2019	DSH	2 years	FN	IGRA	Chronic cough
15	Hertfordshire	Feb 2019	DSH	6 years	MN	IGRA	Weight loss
16	Manchester	Feb 2019	Persian	1 year	MN	IGRA	Respiratory distress
17	Manchester	March 2019	Persian	1 year	MN	IGRA	Chronic cough
18	Manchester	March 2019	Persian	10 months	MN	IGRA	Diarrhoea
19	Manchester	March 2019	Persian	1 year	FE	IGRA	Diarrhoea
20	Manchester	March 2019	Persian	1.5 years	FN	IGRA	Vomiting and diarrhoea
21	Manchester	March 2019	Ragdoll	9 year	MN	IGRA	Weight loss
22	Cheshire	March 2019	Persian	1 year	FE	IGRA	Mild respiratory disease noted by veterinarian[b]
23	Glasgow	March 2019	DSH	1.5 years	MN	Culture	Chronic purulent skin lesion
24	Glasgow	March 2019	DSH	1.5 years	MN	IGRA	Sub-clinical lung disease[c]
25	Cheshire	March 2019	DSH	2 years	FN	PCR	Ulcerated skin mass
26	Dumfries	April 2019	Maine Coon	3 years	ME	PCR and IGRA	Weight loss and pyrexia
27	Cheshire	April 2019	Persian	1 year	FN	IGRA	Subclinical lung disease[c]
28	Lancashire	April 2019	British Shorthair	1 year	MN	IGRA	Weight loss
29	Merseyside	April 2019	Persian	1 year	MN	PCR	Lethargy and lymphadenomegaly
30	Surrey	April 2019	British Blue	3 year	FE	Culture and IGRA	Lethargy, pyrexia and weight loss
31	Aberdeenshire	April 2019	Bengal	4 years	FN	PCR and IGRA	Mild respiratory disease noted by veterinarian[b]
32	Cardiff	April 2019	Bengal	2 years	MN	IGRA	Abdominal mass
33	Devon	April 2019	Maine Coon	6 months	MN	IGRA	Mild respiratory disease noted by veterinarian[b]
34	Glasgow	April 2019	British Shorthair	3 year	MN	IGRA	Haemoptysis
35	Suffolk	April 2019	Bengal	5 years	FE	PCR and IGRA	Lethargy, hyporexia and pyrexia
36	Suffolk	May 2019	Sphinx	5 years	FE	IGRA	Abdominal mass
37	Hampshire	May 2019	Maine Coon	3 years	ME	IGRA	Ascites

(Continues)

TABLE 1 (Continued)

Case No.	Location (county)	Date[a]	Breed	Age	Sex	Positive mycobacterial tests	Clinical sign(s) noted by the owner(s)
38	Herefordshire	May 2019	DSH	2 years	FE	PCR	Mild respiratory disease noted by veterinarian[b]
39	Suffolk	May 2019	DSH	2 years	ME	IGRA	Weight loss
40	Suffolk	May 2019	Persian	9 months	FE	IGRA	Lethargy and hyporexia
41	Cumbria	May 2019	Persian	9 months	FE	IGRA	Lethargy, hyporexia and pyrexia
42	Oxfordshire	June 2019	Bengal	1 year	MN	PCR	Lymphadenomegaly
43	Yorkshire	June 2019	Maine Coon	1.5 years	ME	IGRA	Chronic cough
44	Lincolnshire	June 2019	Bengal	1.5 years	MN	IGRA	Ulcerated skin mass
45	Lincolnshire	June 2019	Bengal	1.5 years	MN	IGRA	Ulcerated skin mass
46	Surrey	July 201	DSH	2 years	MN	Culture	Weight loss and lethargy
47	Cambridgeshire	July 2019	DSH	1.5 years	FN	Culture	Weight loss and lameness

[a]Date is defined as the month the patient was presented to its general practitioner veterinarian with clinical signs of, or owner concerns regarding, possible tuberculosis.

[b]Four cats showed mild clinical signs that were not initially observed by the owners but were noted on clinical examination by the attending veterinary surgeon.

[c]Two cats showed no active clinical signs of disease but did have structural disease consistent with possible mycobacterial infection noted on radiographs.

The clinical abnormality most frequently reported by the examining veterinary surgeons was "respiratory signs", which was recorded in 72.3% (34/47) of cases. The severity of these signs ranged from mild increases in respiratory rate and/or effort, through to a persistent cough and pneumonia, causing life-threatening dyspnoea; it was the recorded reason for euthanasia in two cases (Figure 2a,b). In a further three cases (6.4%), thoracic lymphadenomegaly of the peribronchial, sternal and/or mediastinal lymph nodes was the only gross lesion detected on investigation of the primary presenting complaint (lethargy in two cats and hyporexia in one cat).

Abdominal masses (which were confirmed to be granulomas following further testing) were palpable in 23 of the 47 cats (48.9%), whilst the abdominal viscera (excluding lymph nodes) were found to be structurally abnormal (either enlarged and/or containing granulomatous lesions, Figure 3) in a further four cases (8.2%) as visualized by abdominal radiography, ultrasonography and/or computed tomography (Figure 4). The abdominal lymph nodes associated with the alimentary system (Figure 5) were enlarged in four cats (8.2%) and enlarged as part of a generalized lymphadenomegaly in a further eight cats; hence, 12 cases (25.5%) had abdominal lymphadenomegaly. All cats had a minimum of abdominal radiography, so while significant organomegaly should have been detected, lymphadenomegaly may have been missed in those cats that did not have concurrent abdominal ultrasonography. Overall, *ante mortem* diagnostic imaging of the alimentary tract and associated structures were found to contain gross pathology in 31 of the 47 cases (66.0%), but clinical signs directly relatable to the gastrointestinal system (vomiting, diarrhoea or constipation) were the main presenting sign in only six cats (12.8%).

Uncommon clinical signs included non-healing skin lesions (Figure 6) in four cats (8.2%), orthopaedic involvement in two cats (4.1%) and optic disease (Figure 7) in two cats (4.1%).

At clinical examination pyrexia was noted in 17 cats (36.2%); where recorded, the temperature ranged from 39.8°C to 41.1°C, with a median of 40.0°C (reference interval: 37.7–39.1°C). Routine haematological evaluation was conducted in all of the 47 cats and revealed a non-regenerative anaemia in ten cats (21.3%) and a mild-to-moderate mature neutrophilia in six cats (12.8%). Serum biochemistry was also assessed in all 47 actively infected cats and was largely unremarkable; only two cats (4.1%) showed increased liver enzyme activity, affecting both alanine aminotransferase and alkaline phosphatase. One of these cats had a large hepatic granuloma extending into the biliary duct, whilst the cause of these increases was not identified in the second cat.

In the 12 cats that were tested for feline leukaemia virus (FeLV) antigen and anti-feline immunodeficiency virus (FIV) antibodies, all cats were found to be negative.

2.3 | Mycobacterial testing

Specialist mycobacterial culture and subsequent genotyping at a national reference laboratory (Animal and Plant Health Agency [APHA], Weybridge in the UK) using the approved standardized protocol remain the only test that can result in official confirmation of *M. bovis* infection of companion animals in the UK (Kamerbeek et al., 1997; Middlemiss & Clark, 2018). The APHA protocol for genetic identification of strains is the same used for bovine tuberculosis in cattle in the UK, comprised of spoligotyping according

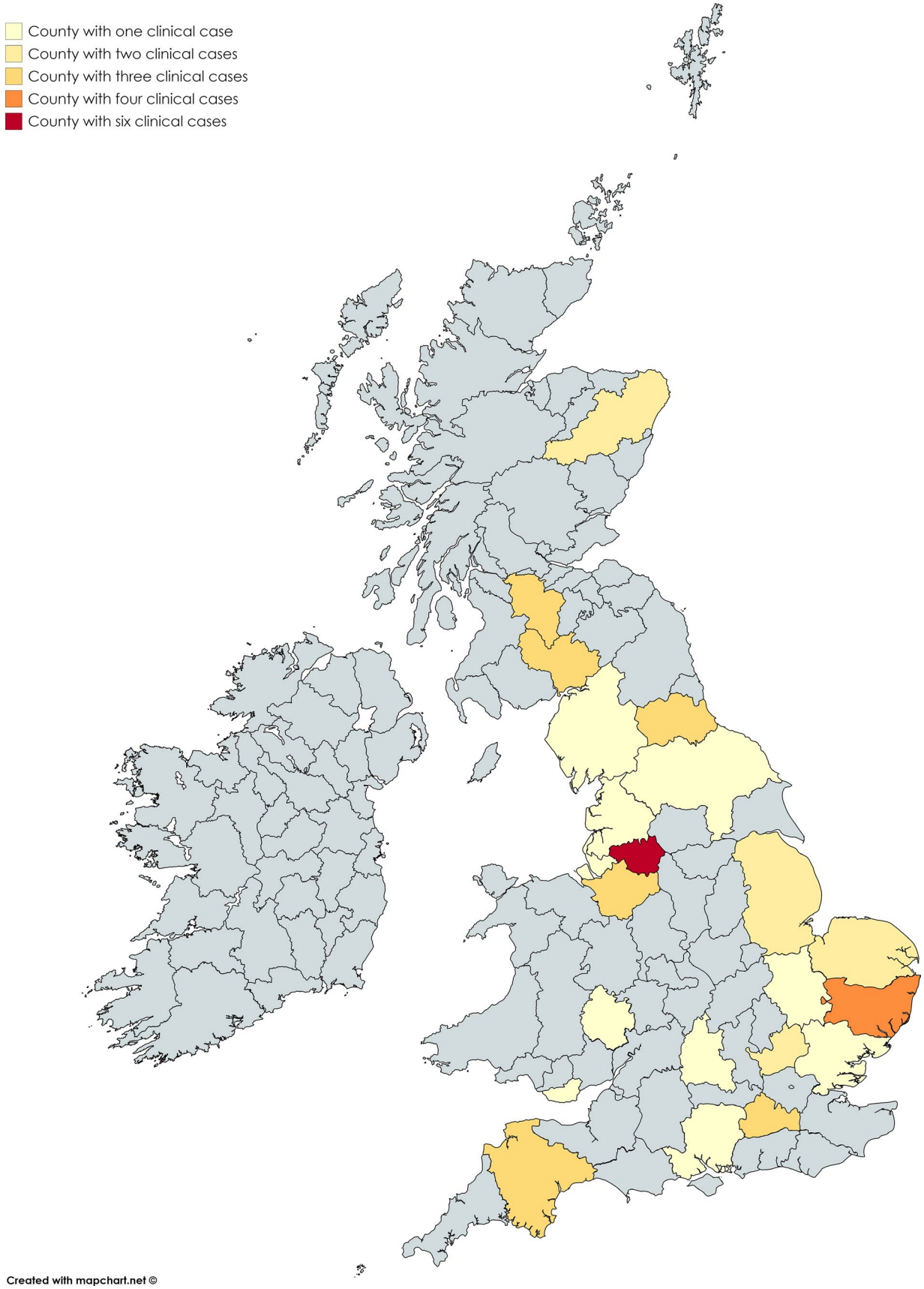

FIGURE 1 A map of the UK showing the distribution of 45 active clinical cases and 2 inactive clinical cases of *M. bovis* infection in domestic cats associated with the consumption of a specific raw food diet

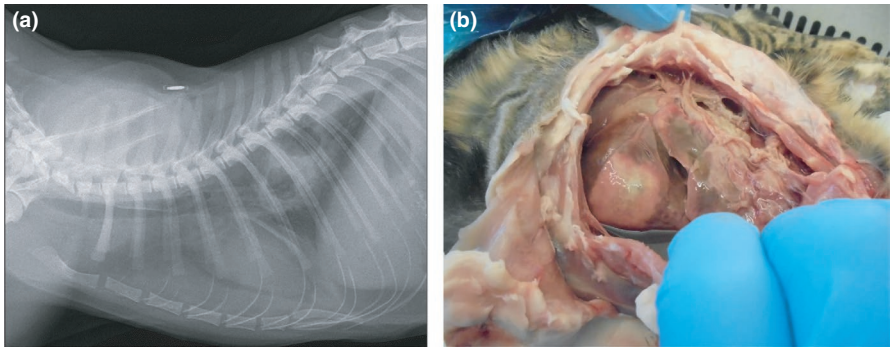

FIGURE 2 (a) A latero-lateral thoracic radiograph of an affected cat (a four-year-old female neutered indoor-only Bengal cat) showing two cavitating lesions within the lower respiratory tract. The cat deteriorated clinically and was euthanized on welfare grounds. (b): *Post-mortem* examination of the same cat revealed extensive fibrinopurulent exudate in the thoracic cavity and the extent of the granulomatous lesions. Lung samples submitted for mycobacterial culture were positive for *M. bovis* 10:a

to the variable number of tandem repeat (VNTR) results and subsequent mycobacterial interspersed repeat units as established by Kamerbeek et al. (1997), updated by Smith and Upton (2011) and widely utilized and described elsewhere (Frothingham and Meeker-O'Connell, 1998; Roring et al., 2002; Skuce et al., 2002).

From this outbreak, grossly diseased tissue samples from eleven cats were obtained at *post-mortem* examination and submitted for mycobacterial culture at APHA Weybridge. All *post-mortem* examinations were conducted either at APHA veterinary investigation centres by APHA pathologists or at the Roslin Institute, University of Edinburgh, under Containment Level 3 conditions by the authors (COH/JH). Five of the eleven cultures (45.5%) resulted in positive results, and genotype analysis has identified all five isolates as genotype 10:a. The five cats were resident across the UK in households located in Scotland and the LRA of England.

Remaining food samples were requested from owners of affected cats, and five were sent to the team at the Roslin Institute, Edinburgh. Culture of viable *M. bovis* was attempted as previously described (O'Halloran et al., 2019); briefly, inside a Containment Level 3 (CL3) laboratory up to 20 g of tissue was homogenized, decontaminated with 5% oxalic acid or 10% sodium hydroxide, and centrifuged, and the pellet was resuspended in sterile phosphate-buffered saline (PBS) and centrifuged again. The homogenate was then resuspended in PBS and sown onto solid Middlebrook 7H11 OADC (Sigma, UK) and liquid Middlebrook 7H9 ADC (Sigma, UK) culture media. Cultures were read at 6 weeks of incubation and again at 14 weeks in order to allow sufficient time required for slow-growing mycobacteria MTBC to produce colonies if viable *M. bovis* was present in the tissue sample.

FIGURE 3 The spleen of an 18-month-old male neutered Burmese cat at laparotomy showing multifocal raised white-pink circular lesions later confirmed as granulomatous on histopathology; they contained acid-fast bacilli with mycobacterial morphology. The liver of this cat was similarly affected

Although it is the reference standard test, mycobacterial culture does have a number of limitations. For example, as a prerequisite it requires the acquisition and submission of fresh or frozen biopsy samples; however, given the location of many of the lesions inside body cavities (i.e., the chest and abdomen) this made retrieving enough sample for culture *ante mortem* an invasive procedure that many of these cases were not clinically fit to undergo. For most of these cats, it was only possible to obtain very small samples by needle aspiration for cytological examination. In a number of cases where larger biopsies had been obtained, they had been formalin-fixed and submitted for histopathological examination and as such were unavailable for culture. For all of the fixed samples, we utilized molecular testing methods (GenoType MTBC; Hain Lifescience GmbH, Germany) at Leeds University Teaching Hospital. This molecular methodology is used as standard of care in the diagnosis of human tuberculosis in the UK, and although not specifically validated for companion animal (tissue) samples, this assay is able to diagnose human mycobacterial infections with MTBC organisms; specific gene probes are then used to determine the infecting species within this group, including the identification of *M. bovis* (National Institute for Health & Care Excellence, 2016). Twelve of the 15 cat samples tested generated positive PCR test results for the presence of mycobacterial DNA; further analysis revealed one infection with an MTBC organism (but there was insufficient DNA for narrower speciation), and 11 were identified to the species level as *M. bovis* infections. Two of the *M.*

FIGURE 4 Ultrasound examination of an 18-month-old male neutered indoor-only Maine Coon cat showing an approximately 2 × 2.5 cm mass in the abdominal cavity

FIGURE 5 A markedly enlarged mesenteric lymph node from the same cat as Figure 4 seen during the laparotomy

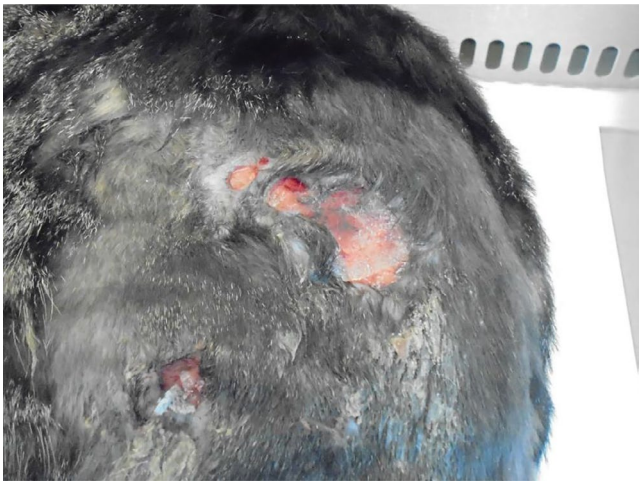

FIGURE 6 The non-healing skin wound over the left pelvis of a two-year-old male, indoor-only, neutered domestic shorthair cat that was subsequently culture-positive for *M. bovis* 10:a

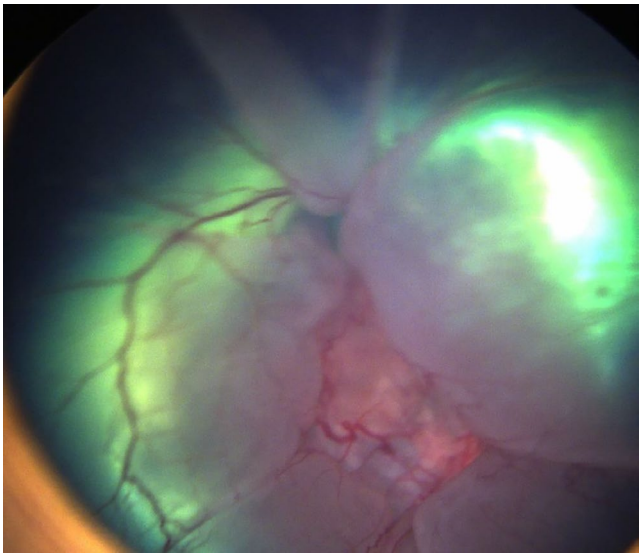

FIGURE 7 Ocular examination of a two-year-old indoor-only female neutered British Shorthair cat presented for conjunctival hyperaemia revealed a highly vascular mass over the optic nerve, later diagnosed (following enucleation) as granulomatous chorioretinitis with acid-fast bacilli, plus associated retinal detachment

bovis-positive test results were subsequently confirmed by mycobacterial culture of contemporaneously obtained visibly lesioned tissue samples.

The cat identified by PCR as being infected with an MTBC organism but with insufficient DNA for speciation was included in this outbreak investigation even though further molecular testing was not possible. This cat was an 18-month-old indoor-only domestic shorthair which had been fed exclusively on the implicated diet since its acquisition by the owners at eight weeks of age, it had a contemporaneous interferon-gamma release assay (IGRA) result strongly suggestive of *M. bovis* infection, as well as lymph node aspirate cytology which confirmed the presence of acid-fast bacilli with mycobacterial morphology. Cumulatively, these findings were taken to support its inclusion as an affected cat.

Immunodiagnostic assays for the diagnosis of tuberculosis are used globally to test human and bovine populations (McCormick-Baw et al., 2018; Wood & Jones, 2001). The most successful of these to date is the IGRA; first developed to aid in the eradication of *M. bovis* from cattle populations in Australia, the assay detects antigen-specific T-cell responses to mycobacterial antigens from circulating leucocytes

to diagnose infection (Rothel et al., 1992; Wood & Jones, 2001). This first test, the BOVIGAM® assay, is now widely used to detect the cell-mediated immune response to *M. bovis* in cattle, sheep, goats, buffalo and bison (Anusz et al., 2017; Pesciaroli et al., 2014; Wood & Jones, 2001). With small adaptations, the test protocol has proved to be extremely useful in humans, and the WHO's new 2018 guidelines on the management of human tuberculosis now support the global use of IGRA testing at-risk populations (Chee et al., 2018; McCormick-Baw et al., 2018). In 2008, adaptations to the test procedure were undertaken by the TB Research Group at the then Veterinary Laboratories Agency (now APHA), to optimize the test for domestic cats (Rhodes et al., 2008a). The resultant feline IGRA is now commercially available via Biobest Laboratories, Edinburgh, UK, and although the number of tested cats remains too small to allow official validation to World Organisation for Animal Health (OIE) standards, several publications have indicated that this is a useful test to generate rapid information on the infection status of cats (Gunn-Moore, 2014; Rhodes et al., 2008b; Rhodes et al., 2011). The methodology and interpretation of this test have been previously published, and the same protocol was used to test cats involved in this outbreak (O'Halloran et al., 2019; Rhodes et al., 2008a). Of particular relevance to this investigation is that this test is currently the cheapest option available to owners. The combination of lack of invasiveness, speed of generating results and lower cost may explain the high number of IGRA tests in this instance rather than the validated reference standard culture.

In a previous *M. bovis* outbreak, we utilized an IGRA for screening apparently healthy kennel-housed Foxhounds with a similar test protocol to the feline IGRA (O'Halloran, Hope et al., 2018). We considered that a positive interferon-gamma response to purified protein derived (PPD) from *M. bovis* (PPDB) was indicative of a significant antigen-specific T-cell response to MTBC bacteria. Such a response was thought to be suggestive of significant challenge and probable infection, rather than just exposure to these mycobacteria. We applied the same criteria to the cats in this outbreak and advised that the 83 IGRA-positive but apparently clinically healthy cats should be further evaluated for the presence of lesions by full clinical examination and diagnostic imaging. As was the case for the Foxhounds, none of these cats showed a significant response to PPD from *M. avium*. The IGRA responses were deemed to be indicative of *M. bovis* infection in cats where there was a response to the peptide cocktail of ESAT-6/CFP-10 as well as PPDB.

During this outbreak, 44 of the 47 clinical cases were tested by IGRA, of which 40 (90.9%) tested positive by the above definition. Of these, eight cases were supported or confirmed by either PCR test (five cats) or subsequent positive cultures (three cats).

2.4 | Sub-clinical and latent cases

As the outbreak continued and the commercial raw diet was implicated, owners who fed their cats the diet became concerned that their cats could be infected. In addition, some of the affected cats lived with other cats, so owners were worried that their other cats could be at risk. Since the IGRA is the only available test for mycobacterial infection that can be performed on an animal with no visible lesions, many of these owners chose to have their cats tested using this assay. At the point of writing, 143 at-risk clinically well cats that had consumed the implicated food had been tested by IGRA, of which 83 (58.0%) gave positive results suggestive of MTBC infections.

Six of the cats (7.2%) were found to have lesions compatible with tuberculosis, as imaging revealed mild interstitial pulmonary disease and associated lymphadenomegaly that were not causing clinical signs as noted by the owners; however, four of the six cats had mild respiratory changes detected by the attending veterinary surgeon (i.e., were active clinical cases); this testing allowed these cats to be treated at an early/mild stage of infection. The additional two cats with no clinical signs (Table 1) but due to the presence of structural disease were designated as active clinical cases and were both treated medically due to the pathology identified.

The remaining 77 cats were IGRA-positive to at least PPDB with no detectable disease. These cats were deemed likely to be sub-clinically or latently infected, and owners were advised that they should be closely monitored for the onset of clinical signs and/or prophylactic therapy could be instigated at their discretion.

2.5 | Public health considerations

The incidence of culture-confirmed zoonotic transmission of *M. bovis* from cats is very rare with only six cases reported in the literature (Isaac, et al., 1983; Lewis-Jonsson, 1946; Roberts et al., 2014; Une & Mori, 2007). However, there may be particular risk to owners who have compromised immune function such as those receiving chemotherapy, radiotherapy or TNF inhibitors (Hofland, et al., 2013; Simonsen, et al., 2017). Therefore, owners of cats with active disease should be advised to seek medical advice if they are at elevated risk and/or if cats have lesions that are discharging (purulent) material or if they have a productive cough.

Owner screening tests (QuantiFERON Gold™ IGRA and/or tuberculin skin tests) conducted to date have identified latent tuberculosis infections (LTBI) in four owners and one vet from seven people tested to the author's knowledge. All of these people had been exposed to severe feline cases with purulent lesions; however, it is unclear whether this represents zoonotic transmission from these cats, infection from handling suspect contaminated food, or whether these individuals were infected at an earlier time with any member of the MTBC (not necessarily *M. bovis*). Public health agencies in the UK have previously assessed the risk to immunocompetent owners from *M. bovis*-infected pets and have concluded that there is "very low" risk of zoonotic transmission (Public Health England, 2014).

3 | EPIDEMIOLOGICAL INVESTIGATION

The only common factor linking these cases was found to be the specific brand of commercial raw cat food consumed by the cats, Natural Instinct Wild Venison, and being mostly indoor cats.

Two breeding colonies were affected; one in the north of England had three clinical cases, plus four clinically well cats (two that were IGRA-positive and two IGRA-negative) in the colony. Tracing rehomed kittens identified ten with severe clinical signs and two that were IGRA-positive but clinically well. The second breeder, located in the south of Scotland, had eight breeding cats of which one was clinically sick (IGRA-positive, culture-negative) and four were clinically well but IGRA-positive. Ten kittens from two litters rehomed from the second breeder were traced; half of these were tested by IGRA, and all five were negative. There were no other common associations between the remaining cats.

With mycobacterial infections, the route of exposure typically leads to infection of the local structures and so disease (usually) presents with clinical signs related to that region. Diagnostic imaging (radiography and/or ultrasonography) of the alimentary tract and associated lymphoid structures were found to contain lesions in 31 of the 47 cases (66.0%) which are consistent with challenge via the gastrointestinal route, supporting the hypothesis of food as the common source of infection. Five cats presented with large lung abscesses, which could be associated with spread via the retropharyngeal lymph nodes having become infected when eating, aspiration of small contaminated food particles whilst eating or may represent dissemination of disease.

All cases were presented to their general practice veterinary surgeons between July 2018 and July 2019. An estimate of the latent period for alimentary infections with tuberculosis in cats is two to five months based on experimental data from the 1900s presented by Francis (1958) in which very large doses (1-10 mg) of *M. bovis* bacilli were given by mouth and produced lesions 40 to 121 days later. Beyond this, the kinetics of feline *M. bovis* infection following oral challenge are unknown. It is likely that in at least some cats, a long sub-clinical/latent phase is seen, as in cattle and humans, and this may extend the upper range of time from infection to disease occurring to many months or even years.

Identifying a likely infection window and determining whether the cats were all infected by one particular batch of contaminated food are difficult questions to answer. The earliest clinical signs were reported in the first weeks of July 2018; if a minimum pre-clinical period is approximately two months, then a contaminated batch of raw pet food manufactured in early May 2018 would be implicated. With the apparent last cases being identified in July 2019, this theoretically includes all batches of food made as late as December 2018 when this product was recalled and production of this product was ceased by the company. With the possibility of long sub-clinical/latent infections adding a considerable degree of open-endedness to the period following infection before signs appear, contaminated batches could theoretically have been produced during the whole of 2018, or even earlier.

An important factor that potentially explains the extended period of this cluster is long storage of the pet food in home freezers. Since the commercial raw diet was marketed with "Limited Availability", owners reported that they tended to bulk purchase when it was available. The freezer shelf life was several months (calculated as nine months from data on packaging) and so a single contaminated batch could feasibly be responsible for this whole cluster. Prior to the recall in December 2018, newly purchased food had a declared shelf life to August 2019. This stored food and that in the freezers of owners who missed the recall may continue to extend the outbreak, albeit at a low level, for many months to come.

Overall, the authors believe that the most likely infection window was probably March to June 2018 and that all cases associated with this raw pet food could fit within this, with stored food and a protracted sub-clinical/latent phase giving rise to later cases. The estimate for a two- to five-month sub-clinical/latent period is supported by the currently observed decline in the presentation of new cases following the recall of the food in December 2018.

Other potential routes of infection were investigated and excluded. Transmission to the cats from the local environment was considered to be very unlikely because a) the cats were kept indoors, with only a few cats having limited, usually supervised, outdoor access, and b) the majority of cases were located in areas of low bovine TB incidence. Infected vermin entering the houses cannot be ruled out for cases in only two households located in the HRA. However, they were not in regions with endemic *M. bovis* genotype 10:a infections in cattle.

Most owners of pedigree cats were located in the LRA and obtained kittens from the LRA, but other cats in the same households had prior ownership which could not be fully investigated, so they could have had previous outdoor access in the HRA. Some of the non-pedigree cats had vague histories, including an in-contact cat that was obtained from a website with no history at all. Incomplete information creates some uncertainty for several of the cases and failure to confirm infection by the reference standard test for the majority of cases adds a degree of uncertainty as to the true number of *M. bovis* cases seen.

Within this group of 47 clinical cases, *M. bovis* genotype 10:a has been cultured from five cases from different areas of England and Scotland and all from out with the natural home range for this strain indicating that infection did not occur from local wildlife. To confirm the food as the source of these infections, a positive *M. bovis* 10:a culture from pet food obtained from owners could provide definitive evidence of the transmission route. However, batches matching the earlier period of the most likely infection window were, unsurprisingly, no longer available at the time of diagnosis and *M. bovis* has not been isolated from the few later dated samples tested by APHA or the University of Edinburgh to date and this remains a weakness of this investigation.

4 | DISCUSSION

This cluster of cases represents a fully documented outbreak of feline tuberculosis putatively caused by feeding pet cats a contaminated commercial raw food diet. Previous examination of feline mycobacterial cases in the UK showed the highest frequency of infections in non-pedigree male cats with frequently reported hunting

behaviour that then develop skin lesions, probably following inoculation of mycobacteria directly into the site of the lesion (Gunn-Moore et al., 2011a; Gunn-Moore, 2014). By contrast, the majority of cases affected in this outbreak were pedigree or pedigree–cross-breeds (76.6%), most had abdominal disease (66.0%), and there was no statistically significant predilection for males to be affected. All cats were housed indoors with no reported history of hunting behaviour. The reason for the high proportion of pedigree cats affected is potentially that owners of these cats are more likely to feed raw food diets. Although this has not been studied systematically, anecdotal evidence suggests that a growing number of pedigree cat breeders in the UK (and elsewhere) are advocating feeding "biologically appropriate raw food" (BARF) diets to owners acquiring kittens (Handl, 2014; Waters, 2017).

More than half of clinical cases in this outbreak presented with palpable abdominal masses (granulomas) and gastrointestinal lymphadenopathy supporting the hypothesis that this outbreak was due to contaminated food. In a study reporting the clinical presentation of feline mycobacterial infections in the UK out with this outbreak, the only alimentary-associated sign reported was weight loss, identified in 15.8% of cases, none of which had directly palpable masses (Gunn-Moore et al., 2011a). In the current cluster, twice the proportion of affected cats (31.9%) showed declining body weight and/or condition. Additionally, cats in this cluster were frequently anaemic and pyrexic which suggests that there may be a more severe phenotype of disease associated with this cluster than would be expected from sylvatic infections (which are rarely pyrexic; DGM data unpublished). This is also supported by the very high mortality rate reported for the early cases (O'Halloran et al., 2019). The reasons for this are not immediately clear; it may be that these cats were exposed to the largest amount of contamination, or it may be that these cats, being largely pedigree breeds, responded differently to mycobacteria; for example, susceptibility to *M. avium–intracellulare* complex infection and disease has previously been reported in Abyssinian cats (Baral et al., 2006). Alternatively, it may be that certain genotypes of *M. bovis* such as 10:a are particularly virulent in the context of companion animal infections; for example, when the same genotype infected a group of Foxhounds it caused fatal fulminant infections in a number of animals (O'Halloran, Hope, et al., 2018). However, there have been insufficient numbers of cases to provide evidence to support this and further work is needed to investigate the host–pathogen interaction of *M. bovis* strains and companion animals; it may be significant in predicting patient prognosis and qualifying zoonotic risk to owners.

Many of the cats were found to have unexpected respiratory changes. The presence of individual demarcated granulomas appears to be most consistent with primary inhalation of bacilli into the lungs, presumptively as these cats were eating contaminated food. In a number of cases, the pattern of lung pathology was more suggestive of disease spreading from a separate focus (such as the gastrointestinal tract). The interstitial lung pattern seen when imaging these latter cases indicates likely haematogenous spread of infection and influx of inflammatory cells into the lung parenchyma. Importantly, many of the IGRA-positive cats with no detectable respiratory signs reported by owners or on clinical examination but were found to have thoracic pathology on imaging, highlighting the need for veterinary surgeons to investigate cases thoroughly if there are concerns over potential exposure.

The epidemiological investigation into this outbreak has demonstrated that the most likely source of infection of these cats was the consumption of a specific brand of commercial raw food diet and that one contaminated batch or even a single contaminated deer carcass could potentially have been responsible for all of the cases diagnosed. In order to increase the certainty of these investigations, it would have been beneficial to have had a greater number of samples submitted for the reference standard test of mycobacterial culture, as genotyping and sequencing isolates adds significant clarity. However, this was hindered at the start of this outbreak by the lack of state funding for most companion animal samples so that the cost to owners for official confirmation of *M. bovis* infection through APHA is now estimated to be in excess of £500 (including *post-mortem* examination). Many owners saw this as prohibitive; however, there was significantly greater uptake of this option when the decision was taken by APHA to temporarily relax the eligibility criteria for funded submissions after the initial cases presented. As an alternative, owners chose to use non-validated but less costly tests; further work to validate these tests would be beneficial for the investigation of any future outbreaks.

Definitive proof that the implicated raw food was the source of infection in these cats would require the isolation of viable *M. bovis* organisms from a sample of the food from the at-risk period. However, five samples obtained from owner-retained food packages have been tested to date by culture and have been found to be negative. This may have been because the food samples submitted were from the time that the cats were diagnosed rather than the point at which they may have been infected. Additionally, the bulk purchasing of food by owners further creates problems for test sensitivity when large batches of food (several kilograms per household) need examining by culture or PCR. Long periods of freezing may also reduce the sensitivity of mycobacterial culture from samples (DEFRA, 2007).

Given the strong suspicions that these cats were infected by a commercial food product, this poses a critical question with respect to how the product became contaminated. Game animals such as deer from across the UK could be at risk of infection with *M. bovis* or a number of other diseases communicable to humans and animals. As the number of raw pet food products on sale in the UK and elsewhere increases, it is critical that the safety of the meat products used to manufacture them is maintained. Under UK legislation, raw pet food can only be made from slaughterhouse material that was passed fit for humans to eat but is unwanted for commercial reasons: fish by-products from factories and ships that prepare fish for human consumption; material from animals that passed an *ante mortem* test but is unfit for humans to eat, for example liver with fluke; or from game that was passed fit for humans to eat but rejected for commercial reasons, not due to disease. The safety of game entering

the food chain is governed by The Wild Game Meat (Hygiene and Inspection) Regulations 1995 which sets out detailed requirements for carcass inspection and handling prior to the consumption of game meat. However, the Food Standards Agency (FSA) state in the recall of the cat food product implicated in this outbreak that it was because "the ingredients were not inspected in line with EU [European Union] requirements" (FSA, 2018). The inclusion of meat from insufficiently examined carcasses in a raw food product is extremely high risk for the spread of infectious diseases, including the potential for tuberculosis as we have previously documented in hunting hounds. It also exposes anyone working with or handling the product to the risk of disease, such as workers in cutting plants breaking down carcasses with machinery that could easily generate transmissible aerosols of tuberculosis. One other possible route of contamination is that because the whole carcass of a large game animal is not always required for *post-mortem* inspection to certify it as fit for human consumption, lesions may be missed. For example, for deer, the head can be discarded prior to inspection, even though a common location for tuberculous lesions is the palatine tonsils (Waters & Palmer, 2015). Because it is plausible that a single infected deer carcass led to the infection of at least 128 cats in this outbreak, the circumstances demonstrate the critical importance of meat inspection and the essential role of trained meat inspectors to this process for the protection of both human and animal health. Since IGRA was the only way to look for evidence of possible *M. bovis* infection in the cats with no clinical signs, the possibility of false-positive results in this group of cats cannot be excluded; however, the risk of missing a clinically infected cat was felt to outweigh the risk of false positives and as many test-positive cats were investigated further.

In conclusion, this study reports a large outbreak of *M. bovis* tuberculosis in pet cats where there was compelling evidence that a contaminated raw food product was the origin; 47 cats were found to have clinical tuberculosis, while another 83 in-contact cats were found to have positive IGRA responses consistent with MTBC infection but no active disease. Based on our estimates of the approximate time from infection to disease appearing and from the epidemiological investigation, it is possible that a single batch of contaminated food produced in late 2017 or early 2018 resulted in the whole cluster of cases. Four cat owners and one veterinary surgeon were diagnosed with suspected latent TB, potentially due to exposure to infected cats with purulent lesions and/or their contaminated feed, though this remains unproven and the risk posed by *M. bovis*-infected cats to humans is very low. This outbreak demonstrates the critical nature of veterinary meat inspection to maintain food safety for human and animals and poses questions for further research in order to investigate the mechanism of infection and the feline immune response to *M. bovis*.

ACKNOWLEDGEMENTS

We wish to thank all of the veterinarians and owners of these cats for facilitating the investigation and giving permission for the findings to be published. Additional thanks go to the APHA staff who assisted with coordinating the epidemiological investigation and conducting *post-mortem* examinations and laboratory testing: Jeff Jones (APHA Carmarthen), Livio Pittalis & Cornelia Bidewell (APHA Bury St Edmunds), Carlo Bianco & Pedro Sanchez-Cordon (APHA Weybridge), Harriet Stacey (APHA Starcross), Sheila Corrieri (APHA Perth), Malgorzata (Gosia) Dabrowska-Jones (APHA veterinary adviser for non-bovines), Ricardo de la Rua-Domenech (APHA Veterinary Adviser (policy) to Defra TB Programme), Eleftheria Palkopoulou (APHA whole-genome sequence analyses) and Vivienne MacKinnon (Veterinary Lead Field Services North Scotland). Conor O'Halloran is supported by a Biotechnology and Biological Sciences Research Council (BBSRC) studentship (BB/M014894/1). Jordan Mitchell is supported by a BBSRC studentship (BB/M010996/1). Jayne Hope is funded by BBSRC Institute Strategic Programme funding (BB/P013740/1 and BBS/E/D/20002174). The remaining authors received no financial support for the research, authorship and/or publication of this article.

CONFLICT OF INTEREST

The authors declare no conflicts of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: O'Halloran C, Tørnqvist-Johnsen C, Woods G, et al. Feline tuberculosis caused by *Mycobacterium bovis* infection of domestic UK cats associated with feeding a commercial raw food diet. *Transbound Emerg Dis*. 2020;00:1–13. https://doi.org/10.1111/tbed.13889